organophosphorus poisoning would indicate that he contemplated the compounds acting as quickly as possible. This is confirmed by his teaching of parenteral formulations and the fact that the only special feature mentioned with respect to oral compositions is that the active compounds may need protection from stomach acids. Shapiro's patent contains nothing that is any more relevant, focusing in the need for good absorption of its active compounds

The Conte article teaches that for the optimum effect certain drugs such as antiasthmatics, anthistamines, psychotropic and cardiovascular drugs and NSAID's should be administered not only in the right amount and the proper rate but also at the right time. This should be done to meet the specific therapeutic needs "of such diseases which depend upon circadian rhythmicity"(page 1017 heft column lines 29 - 30). He then goes on to describe ways of formulating drugs for treatment of such diseases which seek to assure that the drugs are released at the right time. There is, however, no suggestion that drugs for treatment of other conditions might benefit from being formulated in such special ways.

The first cholinesterase inhibitor safe enough to be widely used was donepezil (Aricept). (Date of approval: November 25, 1996.) In double-blind studies, insomnia was the second most frequent side-effect, occurring in 12% more patients on 10 mg of Aricept than on placebo. (For nausea the difference was 13%.) (Table 2., PDR 2002, p. 2666) This insomnia, recognized as a cholinergic effect (two paragraphs above the table) had been noted as early as 1998. (Rogers, Arch Int Med 158:1021-1031, 1998) Abnormal dreams were also noted as a nervous system adverse event (Table 3, PDR, p. 2667). Despite these nocturnal disturbances, the DOSAGE AND ADMINISTRATION section states "Aricept should be taken in the evening, just prior to retiring." (PDR 2002, p. 2667) As the pharmaceutical company was providing the most widely useful art that had to date been approved in this country, it appears that even with more than ordinary skill in the art, there was no appreciation of the need to give a cholinergic drug during the day rather than at night. In two subsequent double-blind studies, published after the priority date of the present application, sleep disturbance in treated patients again exceeded that in placebo patients. (Mohs, Neurology 57:481-488, 2001; Burns, Dement Geriatr Cogn Disord 10:237-244. 1999).

In another strategy besides the prescribing of sleep medications, Ross and Shua-Haim, (J Am Geriat Soc 46:119-120, 1998) treating two patients who were being treated with Aricept and suffering with nightmares, moved the bedtime dose of Aricept to the morning. However, their report does not discuss the physiological diurnal rhythm of brain cholinergic function, nor does it (or its bibliography) suggest a dosage form that could provide the cholinesterase inhibitor in a physiologic manner.

Giving a drug so as not to counter the body's normal physiology is not one of the rationales cited in Conte for the time-programmed release tablets. One of the rationales is "significant daily variation in pharmacokinetics or drug effects." (p. 1017). Any pharmacokinetic or enzyme inhibition changes which might occur during a circadian cycle are not the object of the present invention. The other rationale cited by Conte is to "fulfil the specific therapeutic needs of such diseases, which depend on circadian rhythmicity..." Alzheimer's is not a disease which waxes and wanes on a circadian schedule. The present invention's purpose is to avoid disturbing the natural physiology of the cholinergic system,

and avoid provoking homeostatic compensations such as receptor downregulation and an increase in the acetylcholinesterase enzyme which is being inhibited. If these counterregulatory phenomena occur (AChE does increase in the spinal fluid of Aricept patients [Davidsson, Neurosci Lett 300:157-160, 2001], and receptors downregulate in rat brain [NDA #20-690, p. 266]), the drug's efficacy can be expected to decrease.

The examiner has the advantage of hindsight, which was not available to the present inventor when she made her invention. The evidence of what was thought at the time is that those skilled in the art of treating Alzheimer's disease, and developing cholinomimetic drugs active in the brain, failed to combine the information from the basic science and the pharmaceutical fields. It is the object of the present invention to do so, with the goal of sensitivity to bodily rhythms and the avoidance of a long-term reduction in efficacy. At the time that the present invention was made, it was not obvious to those skilled in the art that there would be any therapeutic reason to formulate acetylcholinesterase inhibitors in such a way as to delay their release within the body.

Copies of the articles referred to in this response are enclosed for the examiner's convenience.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,

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